KENTUCKY INFLUENZA PANDEMIC RESPONSE PLAN
CLINICAL GUIDELINES SUPPLEMENT IV

SUMMARY OF PUBLIC HEALTH ROLES AND RESPONSIBILITIES FOR CLINICAL GUIDELINES

Interpandemic and Pandemic Alert Periods
Healthcare providers should:

- Be aware of case definitions.
- Know procedures for influenza screening and laboratory testing.
- Know appropriate infection control measures.
- Know appropriate antiviral regimens for influenza A (H5N1) and other novel viruses.
- Notify health departments about suspected or confirmed novel influenza cases and fatalities.
- Collect and forward specimens to designated state and federal laboratories for the diagnosis of novel influenza strains.
- Follow public health recommendation on administration of influenza vaccine.

KDPH and local health department:

- Help educate healthcare providers about novel and pandemic influenza.

The Division of Epidemiology and Health Planning (DEHP) Influenza Coordinator will send guidelines for suspect avian influenza cases to hospital Infection Control Professionals, Local Health Department Surveillance Contacts, Local Health Department and Health Care Provider sentinel sites. Guidelines for reporting and instructions for submitting specimens will be posted on the KDPH Web site, the Health Alert Network, and published in *Kentucky Epidemiologic Notes and Reports.*

- Provide or facilitate testing and investigation of suspected novel influenza cases.

The DEHP will coordinate with the Division of Laboratory Services (DLS) to have specimens sent to the State Public Health Laboratory for testing. If the individual's condition meets the screening criteria, the State Influenza Coordinator will advise the healthcare provider to send the specimen to the State Public Health Laboratory. The State Influenza Coordinator will advise the DLS Virus Laboratory that a specimen is being sent. The DLS will test the specimen by PCR. Specimens will be sent to CDC, if necessary.

- Conduct follow-up of suspected novel influenza cases.

The State Influenza Coordinator will request a faxed copy of the screening form from the healthcare provider, and will facilitate an investigation through the Regional Epidemiologist and the Local Health Department Surveillance Contact, for the purpose of obtaining a detailed history of the suspected case and to identify contacts.

HHS agencies:

- Develop and disseminate recommendations on the use of influenza diagnostic tests, antiviral drugs, and vaccines during an influenza pandemic.
- Develop a national stockpile of antiviral drugs for use during a pandemic.
- Work with state and local health departments to investigate and manage suspected cases of human infection with avian influenza A (H5N1) or other novel strains of influenza.
- Establish case definition and reporting mechanisms.

Pandemic Period

Healthcare providers will:

- Regularly review updates on case definitions, screening, laboratory testing, and treatment algorithms for pandemic influenza.
- Follow recommendations on antiviral and vaccine use from federal, state, and local health agencies.
- Choose antiviral treatment appropriate for circulating influenza strains.
- When antiviral supplies are limited, prescribe antivirals for persons in priority groups where the need and benefit are the greatest.
- Report pandemic influenza cases or fatalities as requested by health departments.
- Collect and forward specimens for ongoing pandemic influenza surveillance as requested to designated state and federal laboratories.
- Report atypical cases, breakthrough infections while on prophylaxis, or any other abnormal cases throughout the duration of the pandemic to public health agencies.
- Follow public health recommendation on administration of influenza vaccine.

KDPH and local health departments:

State and local public health agencies will:

- Update providers regularly as the influenza pandemic unfolds.

  DEHP will provide information to the Cabinet's Communications Office to be used at their discretion. Suggested information is a weekly county chart and map indicating the location and number of cases.

- Provide or facilitate testing and investigation of pandemic influenza cases.

  The DEHP and DLS will coordinate facilitation of testing. The DEHP State Influenza Coordinator will facilitate an investigation in collaboration with the Regional Epidemiologists and the Local Health Department Surveillance Contacts.

- Work with CDC to investigate and report special pandemic situations.

  Regional Epidemiologists and Local Health Department Surveillance Contacts will report their findings to the State Influenza Coordinator, who will communicate these findings to the CDC. The DEHP State Influenza Coordinator will contact and fax screening forms to the CDC DEOC, and obtain an assigned ID/State Number for purposes of tracking information.

- Work with other governmental agencies and non-governmental organizations to ensure effective public health communications.

HHS responsibilities:

- Update and disseminate national guidelines on influenza diagnostic testing and use of antiviral drugs and vaccines during the pandemic.
- Develop a pandemic influenza vaccine.
- Work with healthcare partners to refine clinical management guidelines and issue regular updates on treatment issues.
- Conduct studies to investigate pandemic influenza pathogenesis.
- Monitor pandemic influenza cases for antiviral resistance.
- Monitor antiviral drug use and inventories.
- Collect information on clinical features, outcomes, and treatments.

I. RATIONALE

Healthcare providers play an essential role in the detection of an initial case of novel or pandemic influenza in a community. Early identification and isolation of cases may help slow the spread of influenza. Clinical awareness of novel or pandemic influenza disease can also benefit the individual patient, as rapid initiation of treatment can avert potentially severe complications.

Currently there is a lack of specific clinical findings and commercially available laboratory tests to rapidly distinguish novel or pandemic influenza from seasonal influenza. In addition, it is difficult ahead of time to fully predict the clinical characteristics of a novel or pandemic influenza virus strain or the groups at highest risk for complications.

However, clinical management of patients during pandemic influenza will follow many of the same principles of patient care in cases of interpandemic (i.e. "normal") seasonal strains of influenza. Health care workers will need to know 1) the symptoms of an influenza-like illness, 2) the strains that are circulating in the community, 3) the appropriate tests to diagnose influenza, 4) the appropriate infection control precautions, 5) how to select the correct antiviral medicine, 6) the side effects of the antiviral medicines, and 7) how to prescribe antivirals for prophylaxis (see Vaccine and Antiviral Supplement).

Additional difficulties in managing pandemic influenza include 1) differentiating seasonal strains of influenza from pandemic strains, 2) deciding which antiviral medicine would be most appropriate to use, 3) selecting the populations that would benefit most from antivirals in the face of great demands for a limited supply of antivirals, and 4) selecting the populations that would benefit most from influenza vaccine for the pandemic strain in the face of great demands for a limited supply of that influenza vaccine.

The management of influenza is based primarily on sound clinical judgment regarding the individual patient as well as the availability of local resources, such as rapid diagnostic tests, antiviral drugs, influenza vaccine, and hospital beds. Healthcare providers who are well trained in managing seasonal influenza will be better able to effectively diagnose and care for patients with pandemic influenza.

II. OVERVIEW

The Clinical Guidelines Supplement focuses on the initial screening, assessment, and management of patients who present from the community with fever and/or respiratory symptoms during the Interpandemic, Pandemic Alert, and Pandemic Periods (Box 1, page 13, defines these periods). Boxes, figures, tables, and appendices are incorporated from the November 2005 HHS Pandemic Influenza Plan (http://www.hhs.gov/pandemicflu/plan/pdf/HHSPandemicInfluenzaPlan.pdf).

The Appendices add additional information on the clinical presentation and complications of influenza, the clinical features of human infection with avian influenza A (H5N1) virus, and management of secondary bacterial pneumonia during a pandemic. The appendices also contain Clinician Fact Sheets about influenza and antivirals and a respiratory etiquette poster.

During the Interpandemic and Pandemic Alert Periods, early recognition of illness caused by a novel influenza A virus strain will rely on a **combination of clinical and epidemiologic features**.

During periods in which no human infections with a novel influenza A virus strain have occurred anywhere in the world (Interpandemic Period, phases 1 or 2), or when sporadic cases of animal-to-human transmission or rare instances of limited human-to-human transmission of a novel influenza A virus strain have occurred in the world (Pandemic Alert Period, phases 3 or 4), the risk to travelers is low.

Therefore, when a traveler who is returning from an affected area and develops severe respiratory disease or an influenza-like illness, the likelihood of novel influenza A virus infection is **very low**. In this situation, the possibility of infection with seasonal human influenza viruses in returning travelers is much higher and should be considered, since human influenza A and B viruses circulate worldwide among humans year-round.

However, once local person-to-person transmission of a novel influenza A virus strain has been confirmed (Pandemic Alert Period: Phase 5), the potential for novel influenza A virus infection will be higher in an ill person who has a strong epidemiologic link to the affected area.

During the Pandemic Period (in a setting of high community prevalence), diagnosis will be more **clinically oriented** because the likelihood will be high that any severe febrile respiratory illness is pandemic influenza.

This Clinical Guidelines Supplement is current as of January 2006, and is subject to change as experience is gained. Updates will be provided, as needed, on the Kentucky Department for Public Health Web site (http://chfs.ky.gov/dph) and the CDC Web site (www.cdc.gov/flu/).

Other supplements in the pandemic plan may also cover topics of potential interest to clinicians.

III. CLINICAL GUIDELINES FOR THE INTERPANDEMIC AND PANDEMIC ALERT PERIODS

During Interpandemic and Pandemic Alert Periods, the primary goal is to quickly identify and contain cases of novel influenza. To limit evaluating an overwhelming number of patients, screening criteria should rely on a combination of clinical and epidemiologic features.

Febrile respiratory illnesses are one of the most common reasons for medical evaluation during the winter. Therefore, during the interpandemic and pandemic alert period, febrile illnesses caused by novel influenza strains are expected to be rare. Laboratory testing should be done for those with severe respiratory illness, such as pneumonia. The main features of case detection and clinical management during the Interpandemic and Pandemic Alert Periods are outlined in Figure 1.

A. Criteria for evaluation of patients with possible novel influenza

During the Pandemic Alert Period, human infections with novel influenza A viruses will be uncommon. Therefore, **both clinical and epidemiologic criteria should be met**. The criteria will be updated as needed and posted at www.cdc.gov/flu.

1. Clinical criteria

Any suspected cases of human infection with a novel influenza virus must meet the criteria for influenza-like illness (ILI): **temperature of** >100.4°F **(>38°C) plus one of the following: sore throat, cough, or dyspnea**.

Because of the large number of ILI cases during a typical influenza season, during the Interpandemic and Pandemic Alert Periods laboratory evaluation for novel influenza A viruses is recommended **only** for:

a) Hospitalized patients with severe ILI, including pneumonia, who meet the epidemiologic criteria (see below), or
b) Non-hospitalized patients with ILI and with strong epidemiologic suspicion of novel influenza virus exposure (e.g., direct contact with ill poultry in an affected area, or close contact with a known or suspected human case of novel influenza within 10 days prior to onset of symptoms.).

Recommendations for the evaluation of patients with respiratory illnesses are provided in Box 2. Exceptions to the current clinical criteria are provided in Box 3.

2. Epidemiologic criteria

Epidemiologic criteria for evaluation of patients with possible novel influenza focus on the **risk of exposure** to a novel influenza virus with pandemic potential. Although the incubation period for seasonal influenza ranges from 1 to 4 days, the incubation periods for novel types of influenza are currently unknown and might be longer. Therefore, the maximum interval between potential exposure and symptom onset is set conservatively at 10 days.

Exposure risks — Exposure risks fall into two categories: a) travel and b) occupational.

a) Travel risks: Persons have a travel risk if they have, within 10 days prior to onset of symptoms:

1) recently visited or lived in an area affected by highly pathogenic avian influenza A outbreaks in domestic poultry or where a human case of novel influenza has been confirmed, **and**
2) either had direct contact with poultry, **or**
3) had close contact with a person with confirmed or suspected novel influenza. Updated listings of areas affected by avian influenza A (H5N1) and other current/recent novel strains are provided on the Web sites of the OIE (http://www.oie.int/eng/en_index.htm), WHO (www.who.int/en/), and CDC (www.cdc.gov/flu/).

Direct contact with poultry is defined as: 1) touching birds (well-appearing, sick, or dead), or 2) touching poultry feces or surfaces contaminated with feces, or 3) consuming uncooked poultry products (including blood) in an affected area. Close contact with a person from an infected area with confirmed or suspected novel influenza is defined as being within 3 feet (1 meter) of that person during their illness. Because specific testing for human infection with avian influenza A (H5N1) might not be locally available in an affected area, persons reporting close contact in an affected area with a person suffering from a severe, yet unexplained, respiratory illness should also be evaluated.

Human influenza viruses circulate worldwide and year-round, including in countries with outbreaks of avian influenza A (H5N1) among poultry. Therefore, during the Interpandemic and Pandemic Alert Periods, human influenza virus infection can be a cause of ILI among returned travelers at any time of the year, including during the summer in the United States. This includes travelers returning from areas affected by poultry outbreaks of highly pathogenic avian influenza

A (H5N1) in Asia. As of May 2006, such persons are currently more likely to have infection with human influenza viruses than with avian influenza A (H5N1) viruses.

b) Occupational risks

Persons at occupational risk for infection with a novel strain of influenza include:

1) persons who work on farms or live poultry markets
2) persons who process or handle poultry infected with known or suspected avian influenza viruses
3) workers in laboratories that contain live animal or novel influenza viruses
4) healthcare workers in direct contact with a suspected or confirmed novel influenza case.

Information on limiting occupational risk is provided on the Occupational Health and Safety Administration (OSHA) Web site at: www.osha.gov/dsg/guidance/avian-flu.html.

During the Interpandemic and Pandemic Alert Periods, when there is no sustained human-to-human transmission of any novel influenza viruses, **direct contact** with animals such as poultry in an affected area or close contact with a case of suspected or confirmed human novel influenza is **required** for further evaluation.

During the Pandemic Alert Period, Phases 3 and 4, the majority of human cases of novel influenza will result from avian-to-human transmission (see Box 1). Therefore, a history of direct contact with poultry (well-appearing, sick, or dead), consumption of uncooked poultry or poultry products, or direct exposure to environmental contamination with poultry feces in an affected area will be important to ascertain.

During the Pandemic Alert Period, Phase 5, a history of close contact with an ill person suspected or confirmed to have novel influenza in an affected area will be even more important.

Other avian influenza A viruses

Although the epidemiologic criteria for novel influenza are based on recent human cases of avian influenza A (H5N1), they are intended for use in the evaluation of suspected cases of infection with any novel influenza A virus strain.

Other avian influenza A viruses that have caused human disease include the highly pathogenic viruses H7N7 and H7N3 and the low pathogenic viruses H9N2 and H7N2. Some of these human cases have occurred in Europe (Netherlands) and North America (Canada and the United States). Therefore, the same high-risk exposures defined above for avian influenza A (H5N1) also apply to other avian influenza A viruses.

A strong epidemiologic link to an avian influenza outbreak in poultry, even in areas that have not experienced poultry outbreaks of avian influenza A (H5N1), may raise the index of suspicion for human infection with avian influenza A viruses.

In the future, other animal hosts (in addition to poultry) or novel influenza A virus subtypes (in addition to H5N1) might become significantly associated with human disease. If such events occur, this guidance will be updated.

B. Initial management of patients who meet the criteria for novel influenza

When a patient meets both the clinical and epidemiologic criteria for a suspected case of novel influenza, healthcare personnel should initiate the following activities:

1. Implement infection control precautions for novel influenza, including Respiratory Hygiene/Cough Etiquette. Patients should be placed on **Droplet Precautions** for a **minimum of 5 days** unless there is full resolution of illness or another etiology has been identified before that period has elapsed. Healthcare personnel should wear surgical or procedure **masks** on entering a patient's room, as per Droplet Precautions. They should also wear **gloves**, **eye protection and gowns when indicated** for Standard Precautions (See Infection Control supplement III Table 1). Patients should be admitted to a single-patient room, and patient movement and transport within the hospital should be limited to medically necessary purposes (see also Infection Control Supplement).

2. **Notify the local health department or KDPH**. Report each patient who meets the clinical and epidemiologic criteria for a suspected case of novel influenza to the state or local health department as quickly as possible to facilitate initiation of public health measures (see Laboratory and Surveillance Supplement). Designate one person as a point of contact to update public health authorities on the patient's clinical status.

3. **Obtain clinical specimens** for novel influenza A virus testing and notify the local and state health departments to arrange testing. Testing of suspected novel or pandemic influenza will be directed by public health authorities (see Laboratory and Surveillance Supplement for more detailed guidelines).
    a. Where feasible, collect of the following respiratory specimens for novel influenza A virus testing: 1) nasopharyngeal swab; 2) throat swab; 3) tracheal aspirate (for intubated patients); and 4) nasal swab, aspirate or wash.
    b. Store specimens at 4°C in viral transport media until transported or shipped for testing. Acute (within 7 days of illness onset) and convalescent serum specimens (2–3 weeks after the acute specimen and at least 3 weeks after illness onset) should be obtained and refrigerated at 4°C or frozen at minus 20–80°C. Serological testing for novel influenza virus infection can be performed only at CDC.
    c. Immediately notify their local health departments of their intention to ship clinical specimens from suspected cases of human infection with a novel influenza A virus, to ensure that the specimens are handled under proper biocontainment conditions.
    d. Novel influenza A viruses can be confirmed by RT-PCR or virus isolation from tissue cell culture with subtyping. However, RT-PCR for testing of novel influenza viruses cannot be performed by a hospital laboratory and is available only at state public health laboratories and CDC. Viral culture of specimens from suspected novel influenza cases should be attempted **only** in laboratories that meet the biocontainment conditions for BSL-3 with enhancements or higher.
    e. Rapid influenza diagnostic tests and immunofluorescence (indirect fluorescent antibody staining [IFA] or direct fluorescent antibody staining [DFA]) may be used to detect seasonal influenza, but **should not be used to confirm or exclude novel influenza during the Pandemic Alert Period**. Rapid influenza tests have relatively low sensitivity for detecting seasonal influenza, and their ability to detect novel influenza subtypes is unknown. Such tests can identify influenza A viruses but cannot distinguish between human infection with seasonal and novel influenza A viruses. A negative rapid influenza test result does **not** necessarily

exclude human infection with either seasonal or novel influenza A viruses. A positive rapid influenza test result could be a false positive or represent infection with either seasonal or novel influenza A viruses. Therefore, both negative and positive rapid influenza test and immunofluorescence results should be interpreted with caution, and RT-PCR testing for influenza viruses should be performed. (See Laboratory and Surveillance Clinical Guidelines Supplement for further information on rapid diagnostic testing).

f. Acute and convalescent serum samples and other available clinical specimens (respiratory, blood, and stool) should be saved and refrigerated or frozen for additional testing until a specific diagnosis is made.

4. **Evaluate alternative diagnoses**. An alternative diagnosis should be based only on laboratory tests with high positive-predictive value (e.g., blood culture, viral culture, PCR, Legionella urinary antigen, pleural fluid culture, transthoracic aspirate culture). If an alternate etiology is identified, the possibility of **co-infection** with a novel influenza virus may still be considered if there is a strong epidemiologic link to exposure to novel influenza.

5. **Decide on inpatient or outpatient management**. The decision to hospitalize a suspected novel influenza case will be based on the physician's clinical assessment and assessment of risk and whether adequate precautions can be taken at home to prevent the potential spread of infection.
    a. Patients cared for at home should be separated from other household members as much as possible.
    b. All household members should carefully follow recommendations for hand hygiene, and tissues used by the ill patient should be placed in a bag and disposed with other household waste (Box 4).
    c. Although no studies have assessed the use of masks at home to decrease the spread of infection, use of surgical or procedure masks by the patient and/or caregiver during interactions may be of benefit.
    d. Separation of eating utensils for use by a patient with influenza is not necessary, as long as they are washed with warm water and soap (Box 4).

6. **Initiate antiviral treatment as soon as possible**, even if laboratory results are not yet available. Clinical trials have shown that these drugs can decrease the illness due to seasonal influenza duration by several days when they are initiated **within 48 hours of illness onset**. The clinical effectiveness of antiviral drugs for treatment of novel influenza is unknown, but it is likely that the earlier treatment is initiated, the greater the likelihood of benefit. During the Pandemic Alert Period, available virus isolates from any case of novel influenza will be tested for resistance to the currently licensed antiviral medications. (See Vaccine and Antiviral Supplement for antiviral information).

7. **Assist public health officials with identifying exposed contacts**. After consulting with KDPH or local public health officials, clinicians might be asked to help identify persons exposed to the suspected novel influenza case-patient (particularly healthcare workers). In general, persons in close contact with the case-patient at any time beginning one day before the onset of illness are considered at risk. Close contacts might include household and social contacts, family members, workplace or school contacts, fellow travelers, and/or healthcare providers.

C. Management of patients who test positive for novel influenza

If a patient is confirmed to have an infection with a novel influenza virus:

1. Continue antiviral treatment
2. Continue all isolation and infection control precautions
3. Isolate patients with novel influenza from seasonal influenza patients.

In addition to prior vaccination against seasonal influenza, such measures may decrease the risk of co-infection and viral genetic reassortment.

D. Management of patients who test positive for seasonal influenza

Many people who are suspected to have a novel influenza will be found to have seasonal human influenza, particularly during the winter season. It should be recognized that human influenza viruses circulate among people worldwide throughout the year, including in affected areas with poultry outbreaks of avian influenza A viruses.

For patients with confirmed seasonal influenza, maintain Standard and Droplet Precautions, and continue appropriate antiviral treatment for a full treatment course (e.g., 5 days).

E. Management of patients who test negative for novel influenza

The sensitivity of the currently available tests for detecting novel influenza viruses in clinical specimens has not been thoroughly evaluated, so false-negative test results may occur. Therefore, if test results are negative but the clinical and epidemiologic suspicion for a novel influenza virus remains high, continue antiviral treatment and isolation procedures. Test results could be negative for influenza viruses for several reasons:

1. Some patients may have an alternate etiology to explain their illness. The general work-up for febrile respiratory illnesses described below should evaluate the most common alternate causes.
2. A certain number of truly infected cases might also test falsely negative, due to specimen collection conditions, to viral shedding that is not detectable, or to sensitivity of the test.

Interpretation of negative testing results should be tailored to the individual patient in consultation with hospital infection control and infectious disease specialists, as well as the state or local health department and CDC. In hospitalized patients who test negative for novel influenza but have no alternate diagnosis established, novel-influenza-directed management should be continued if clinical suspicion is high and there is a strong epidemiologic link to exposure to novel influenza.

When influenza tests are negative and an alternative diagnosis is established, isolation precautions and antiviral drug therapy for novel influenza may be discontinued based on clinician's assessment if:

1. There is no strong epidemiologic link
2. An alternative diagnosis is made using a test with a high positive-predictive value
3. The clinical manifestations are explained by the alternative diagnosis.

IV. CLINICAL GUIDELINES FOR THE PANDEMIC PERIOD

During the Pandemic Period, the primary goal of rapid detection is to appropriately identify and triage cases of pandemic influenza. During this period, outpatient clinics and emergency departments might be overwhelmed with suspected cases, restricting the time and laboratory

resources available for evaluation. In addition, if the pandemic influenza virus exhibits transmission characteristics similar to those of seasonal influenza viruses, illnesses will likely spread throughout the community too rapidly to allow the identification of obvious exposures or contacts.

Evaluation will therefore focus predominantly on **clinical** and **basic laboratory** findings, with less emphasis on laboratory diagnostic testing (which may be in short supply) and **epidemiologic criteria**. Nevertheless, clinicians in communities without pandemic influenza activity might consider asking patients about recent travel from a community with pandemic influenza activity or close contact with a suspected or confirmed pandemic influenza case. The main features of clinical management during the Pandemic Period are outlined in Figure 2.

A. Criteria for evaluation of patients with possible pandemic influenza

1. Clinical criteria

Suspected cases of pandemic influenza virus infection should meet the criteria for an ILI: **temperature of** >100.4°F (**>38°C) plus one of the following: sore throat, cough, or dyspnea**.

Although past influenza pandemics have most frequently resulted in respiratory illness, the next pandemic influenza virus strain might present with a different clinical syndrome (see Appendix 1 and Appendix 2). During a pandemic, updates on other clinical presentations will be provided at: www.pandemicflu.gov and www.cdc.gov/flu/.

Recommendations for general evaluation of patients with ILI are provided in Box 2. Exceptions to the clinical criteria are provided in Box 3.

2. Epidemiologic criteria

During the Pandemic Period, an exposure history will be marginally useful for clinical management when disease is widespread in a community. In addition, there will be a relatively high likelihood that any case of ILI during that time period will be pandemic influenza. Once pandemic influenza has arrived in a particular locality, **clinical criteria will be sufficient** for classifying the patient as a **suspected** pandemic influenza case.

B. Initial management of patients who meet the criteria for pandemic influenza

When a patient meets the criteria for a suspected case of pandemic influenza, healthcare personnel should initiate the following activities:

1. **Report** according to local and state health department recommendations for patients who meet the criteria for pandemic influenza. See Clinical Guidelines Supplement1 for guidance on case reporting during the Pandemic Period.
2. If the patient is hospitalized, implement **infection control precautions** for pandemic influenza, including Respiratory Hygiene/Cough Etiquette (see Infection Control Supplement, Box 2).
    a. Place the patient on Droplet Precautions for a minimum of 5 days from the onset of symptoms.
    b. Healthcare personnel should wear surgical or procedure masks on entering a patient's room, as per Droplet Precautions
    c. Healthcare personnel should wear gloves and gowns, when indicated, as per Standard Precautions (Box 1, Infection Control Supplement 3).

d. Patients should be admitted to either a single-patient room or an area designated for cohorting of patients with influenza.
e. Patient movement and transport outside the isolation area should be limited to medically necessary purposes (see Table 1, Infection Control).

3. **Limit hospital admission** of patients should be limited to those with severe complications who cannot be cared for outside the hospital setting, especially once a pandemic is underway.

4. Obtain **clinical specimens**, as clinically indicated (see Box 2).
   a. Once pandemic influenza has arrived in a community, influenza testing will likely not be needed for most patients.
   b. Work in conjunction with health departments to perform laboratory testing in a subset of pandemic influenza cases, as part of ongoing virologic surveillance (see Laboratory and Surveillance Supplement).
   c. Influenza diagnostic testing should be considered before initiating treatment with antivirals (see Vaccine and Antiviral Supplement).
   d. See Laboratory and Surveillance Supplement for guidelines for pandemic influenza virus testing.
   e. As with seasonal influenza, RT-PCR and virus isolation from tissue culture will be the most accurate methods for diagnosing pandemic influenza.
   f. Specimens should generally include combined nasopharyngeal aspirates or nasal swabs, and throat swabs, stored at 4°C in viral transport media.
   g. BSL-2 conditions should be sufficient for viral culture of clinical specimens from suspected pandemic influenza patients during the Pandemic Period.

5. **Know how to properly use rapid diagnostic tests** for influenza
   a. Rapid tests and immunofluorescence may be helpful for initial clinical management, including cohorting and treatment, but have relatively low sensitivity for detecting seasonal influenza, and their ability to detect pandemic influenza viruses is unknown.
   b. The sensitivity of rapid diagnostic tests will likely be higher in specimens collected within two days of illness onset, in children, and when tested at clinical laboratories that perform a high volume of testing.
   c. During a pandemic a negative rapid test may be a false negative. Therefore test results need to be interpreted within the overall clinical context. For example, it may not be optimal to withhold antiviral treatment from a seriously ill high-risk patient on the basis of a negative test; however, in a setting of limited antiviral drug availability, treatment decisions in less high-risk situations could be based on test results.
   d. The risk of a false-negative test also must be taken into account in making cohorting decisions.
   e. Rapid diagnostic testing should not preclude more reliable testing, if available.
   f. See Laboratory and Surveillance Clinical Guidelines Supplement for further information on rapid diagnostic testing.

6. **Decide on inpatient or outpatient management**. The decision to hospitalize a suspected pandemic influenza case will be based on the physician's clinical assessment of the patient as well as the availability of hospital beds and personnel. Guidelines on cohorting and infection control for admitted patients can be found in Infection Control Supplement.

a. High priority for admission
    i. An unstable patient.
    ii. Patients with high-risk conditions (see Appendix 1) might also warrant special attention, such as observation or close follow-up, even if disease is mild.
b. Appropriate for home management with follow-up.
    i. Well-appearing young children with fever alone.
c. See Vaccine and Antiviral Supplement for inpatient and outpatient antiviral treatment strategies.

7. **Infection control for home care**
    a. Patients cared for at home should be separated from other household members as much as possible.
    b. All household members should carefully follow recommendations for hand hygiene, and tissues used by the ill patient should be placed in a bag and disposed with other household waste (Box 4).
    c. Infection within the household may be minimized if a primary caregiver is designated. The primary caregiver would ideally be someone who does not have an underlying condition that places them at increased risk of severe influenza disease.
    d. Using a surgical or procedure mask by the patient or caregiver during interactions may be of benefit.
    e. Separation of eating utensils for use by a patient with influenza is not necessary, as long as they are washed with warm water and soap (Box 4).

C. Clinical management of pandemic influenza patients

See Vaccine and Antiviral Supplement for current antiviral information and treatment strategies. In addition to the use of antivirals, clinical management of severe influenza should address supportive care and the rapid identification and treatment of secondary complications.*

1. Provide CDC with virus isolates from persons who fail treatment or antiviral prophylaxis, as these strains may more likely be drug resistant.
2. Do not give aspirin or other salicylate-containing product to children aged < 18 years with suspected or confirmed pandemic influenza because of an increased risk of Reye syndrome in this age group (characterized by acute encephalopathy and liver failure).
3. Monitor for complications. Complications related to seasonal human influenza occur more commonly in persons with certain underlying medical conditions, such as chronic respiratory or cardiovascular disease and extremes of age, and are described in Appendix 1. Limited data are available on risk factors and complications related to infection with novel influenza viruses, and these may change as individual strains evolve.
4. Review the summary of the clinical presentations and complications associated with recent influenza A (H5N1) viruses in Appendix 2.
5. Be aware that post-influenza community-acquired pneumonia will likely be a commonly encountered complication, and be aware of recommended methods for diagnosis and treatment. Guidance on the management of influenza-related pneumonia is in Appendix 3.

- Ribavirin and immunomodulatory therapies, such as steroids, are <u>not</u> approved by the FDA for treatment of severe influenza of any type and are investigational at this time.

These agents frequently have severe adverse effects, such as bone marrow and hepatic toxicity, while the benefits of these therapies are unknown.

Box 1. Risk of Novel Influenza in Persons with Severe Respiratory Disease or Influenza-like Illness during the Interpandemic and Pandemic Alert Periods

Clinicians should recognize that human influenza A and B viruses and other respiratory viruses circulate year-round among people throughout the world, including in countries affected by outbreaks of avian influenza A viruses in poultry. Seasonal human influenza A and B community outbreaks occur in temperate climates of the northern and southern hemisphere, and human influenza activity may occur year-round in subtropical and tropical regions. Outbreaks of human influenza can occur among travelers during any time of the year, including periods of low influenza activity in the United States (e.g., summer)

Phases 1, 2: Interpandemic Period
A novel influenza A virus has been detected in animals but not in humans. During these phases, the risk of human infection with a novel influenza A virus strain is extremely low. The risk of human infection with human influenza viruses or other viruses is much higher in persons living in or traveling to affected areas.

Phases 3, 4: Pandemic Alert Period
A novel influenza A virus has been detected in humans through sporadic animal-to-human transmission in an affected area (e.g., direct contact with infected poultry), and few cases of limited, local human-to-human transmission have occurred (small clusters of cases). During these phases, the risk of human infection with a novel influenza A virus strain is very low. The risk of human infection with human influenza viruses or other viruses is much higher in persons living in or traveling to affected areas

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Phase 5: Pandemic Alert Period
A novel influenza A virus has been detected in humans in larger clusters in an affected area, suggesting that the virus is becoming better adapted to spread among people. During this period, the risk of human infection with a novel influenza A virus strain is higher, depending on specific exposures, in persons living in or traveling to affected areas. Human infection with human influenza viruses or other viruses will occur and should still be considered.

Box 2. Clinical Evaluation of Patients with Influenza-like Illness during the Interpandemic and Pandemic Alert Periods

- Patients who require hospitalization for an influenza-like illness for which a definitive alternative diagnosis is not immediately apparent* should be questioned about: 1) travel to an area affected by avian influenza A virus outbreaks in poultry, 2) direct contact with poultry, 3) close contact with persons with suspected or confirmed novel influenza, or 4) occupational exposure to novel influenza viruses (such as through agricultural, health care, or laboratory activities).
- Patients may be screened on admission for recent seasonal influenza vaccination and pneumococcal vaccination. Those without a history of immunization should receive these vaccines before discharge, if indicated.
- Patients meeting the epidemiologic criteria for possible infection with a novel strain of influenza should undergo a routine diagnostic work-up, guided by clinical indications. Appropriate personal protective equipment should be used when evaluating patients with suspected novel influenza, including during collection of specimens.**
- Diagnostic testing for a novel influenza A virus should be initiated as follows:
  - Collect all of the following specimens: nasopharyngeal swab, nasal swab, wash, or aspirate, throat swab, and tracheal aspirate (if intubated), and place into viral transport media and refrigerate at 4°C until specimens can be transported for testing.
  - Immediately contact the local and state health departments to report the suspected case and to arrange novel influenza testing by RT-PCR.

RT-PCR testing is not available in hospital laboratories and must be performed at a qualified laboratory such as a state health department laboratory or the CDC Influenza Laboratory. Viral culture should be performed only at biosafety level 3 [BSL-3] with enhancements (see Laboratory Supplement).

- Depending on the clinical presentation and the patient's underlying health status, other initial diagnostic testing might include:
  - Pulse oximetry
  - Chest radiograph
  - Complete blood count (CBC) with differential
  - Blood cultures
  - Sputum (in adults), tracheal aspirate, and pleural effusion aspirate (if an effusion is present) Gram stain and culture
  - Antibiotic susceptibility testing (encouraged for all bacterial isolates)
  - Multivalent immunofluorescent antibody testing or PCR of nasopharyngeal aspirates or swabs for common viral respiratory pathogens, such as influenza A and B, adenovirus, parainfluenza viruses, and respiratory syncytial virus, particularly in children
  - In adults with radiographic evidence of pneumonia, *Legionella* and pneumococcal urinary antigen testing
  - If clinicians have access to rapid and reliable testing (e.g., PCR) for *M. pneumoniae* and *C. pneumoniae*, adults and children <5 yrs with radiographic pneumonia should be tested.
  - Comprehensive serum chemistry panel, if metabolic derangement or other end-organ involvement such as liver or renal failure is suspected.

*Further evaluation and diagnostic testing should also be considered for outpatients with strong epidemiologic risk factors and mild or moderate illness (see Box 3).

**Healthcare personnel should wear surgical or procedure masks on entering a patient's room (Droplet Precautions), as well as gloves and gowns, when indicated (Standard Precautions) (see Table and Infection Control Supplement).

Box 3. Special Situations and Exceptions to the Clinical Criteria

Persons with a high risk of exposure—For persons with a high risk of exposure to a novel influenza virus (e.g., poultry worker from an affected area,* caregiver of a patient with laboratory-confirmed novel influenza, employee in a laboratory that works with live novel influenza viruses), epidemiologic evidence might be enough to initiate further measures, even if clinical criteria are not fully met. In these persons, early signs and symptoms—such as rhinorrhea, conjunctivitis, chills, rigors, myalgia, headache, and diarrhea—in addition to cough or sore throat, may be used to fulfill the clinical criteria for evaluation.

High-risk groups with atypical symptoms—Young children, elderly patients, patients in long-term care facilities, and persons with underlying chronic illnesses might not have typical influenza-like symptoms, such as fever. When such patients have a strong epidemiologic risk factor, novel influenza should be considered with almost any change in health status, even in the absence of typical clinical features. Conjunctivitis has been reported in patients with influenza A (H7N7) and (H7N3) infections. In young children, gastrointestinal manifestations such as vomiting and diarrhea might be present. Infants may present with fever or apnea alone, without other respiratory symptoms, and should be evaluated if there is an otherwise increased suspicion of novel influenza.

*Updated lists of affected areas are provided at the Web sites of the OIE (http://www.oie.int/eng/en_index.htm), WHO (www.who.int/en/), and CDC (www.cdc.gov/flu/).

Box 4. Home Care Infection Control Guidance for Pandemic Influenza Patients and Household Members

Most patients with pandemic influenza will be able to remain at home during the course of their illness and can be cared for by family members or others who live in the household. Anyone who has been in the household with an influenza patient during the incubation period is at risk for developing influenza. A key objective in this setting is to limit transmission of pandemic influenza within and outside the home.

Management of influenza patients in the home

- Physically separate the patient with influenza from non-ill persons living in the home as much as possible.
- Patients should not leave the home during the period when they are most likely to be infectious to others (i.e., 5 days after onset of symptoms). When movement outside the home is necessary (e.g., for medical care), the patient should follow respiratory hygiene/cough etiquette (i.e., cover the mouth and nose when coughing and sneezing) and should wear a mask.

Management of other persons in the home

- Persons who have not been exposed to pandemic influenza and who are not essential for patient care or support should not enter the home while persons are still having a fever due to pandemic influenza.
- If unexposed persons must enter the home, they should avoid close contact with the patient.
- Persons living in the home with the patient with pandemic influenza should limit contact with the patient to the extent possible; consider designating one person as the primary care provider.
- Household members should be vigilant for the development of influenza symptoms. Consult with healthcare providers to determine whether a pandemic influenza vaccine, if available, or antiviral prophylaxis should be considered.

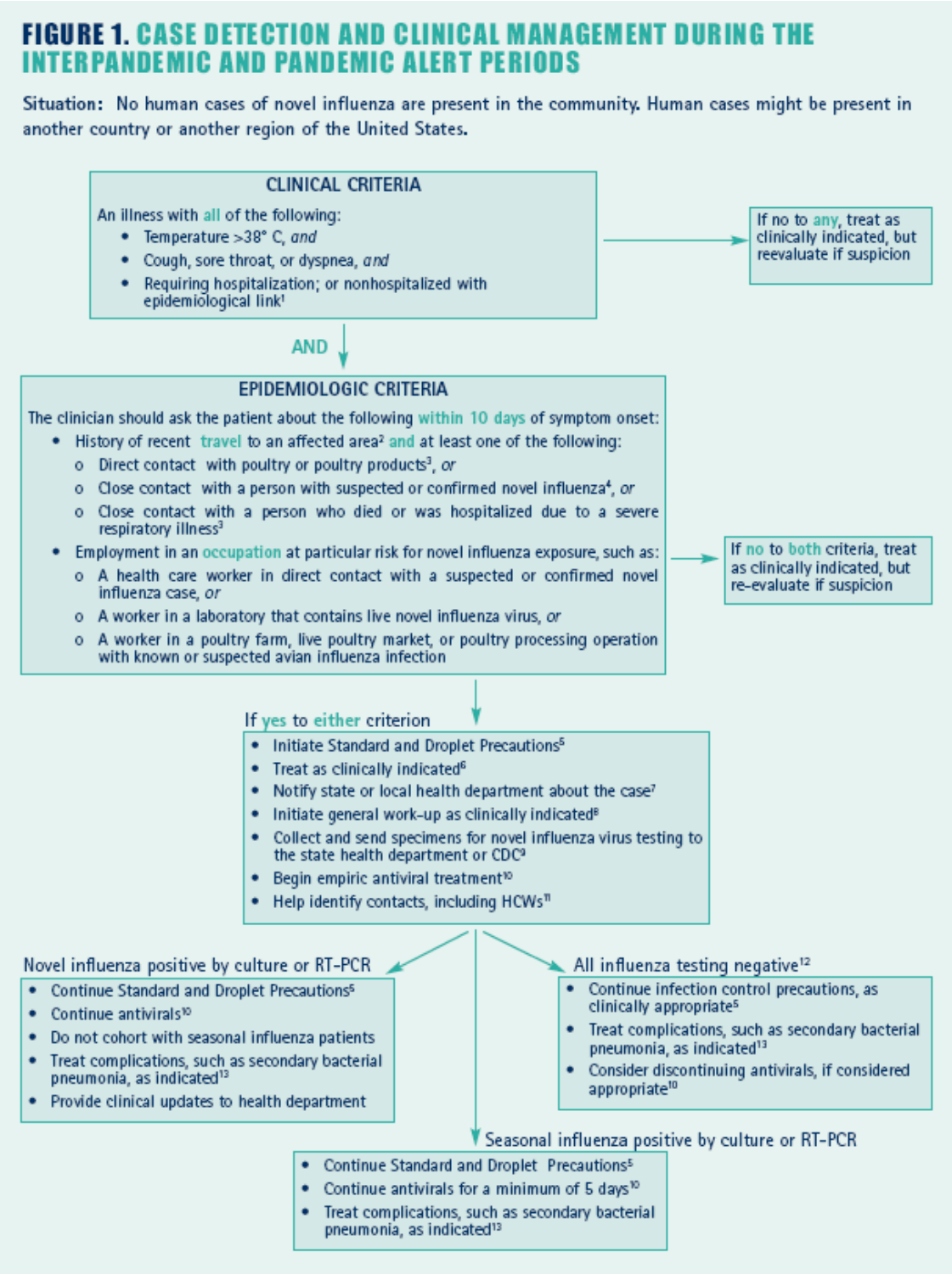
Infection control measures in the home

- All persons in the household should carefully follow recommendations for hand hygiene (i.e., hand washing with soap and water or use of an alcohol-based hand rub) after contact with an influenza patient or the environment in which they are receiving care.
- Although no studies have assessed the use of masks at home to decrease the spread of infection, using a surgical or procedure mask by the patient or caregiver during interactions may be beneficial.
- Soiled dishes and eating utensils should be washed either in a dishwasher or by hand with warm water and soap. Separation of eating utensils for use by a patient with influenza is not necessary.

Box 4. Home Care Infection Control Guidance for Pandemic Influenza Patients and Household Members – con.

- Laundry may be washed in a standard washing machine with warm or cold water and detergent. It is not necessary to separate soiled linen and laundry used by a patient with influenza from other household laundry. Care should be used when handling soiled laundry (i.e., avoid "hugging" the laundry) to avoid self-contamination. Hand hygiene should be performed after handling soiled laundry.
- Tissues used by the ill patient should be placed in a bag and disposed of with other household waste. Consider placing a bag for this purpose at the bedside.
- Environmental surfaces in the home should be cleaned using normal procedures

Figure 1. Case Detection and Clinical Management during the Interpandemic and Pandemic Alert Periods



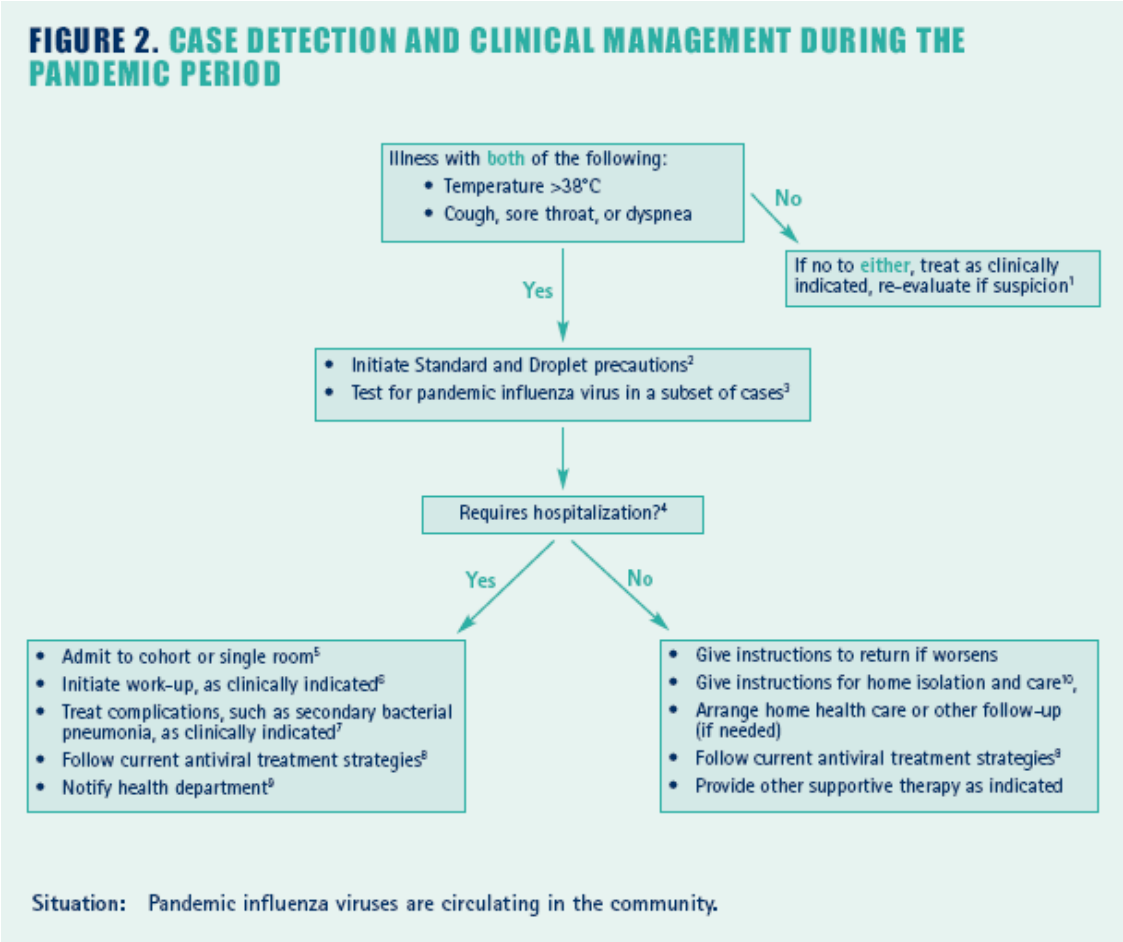
Footnotes to Figure 1:

1. Further evaluation and diagnostic testing should also be considered for outpatients with strong epidemiologic risk factors and mild or moderate illness. (See Box 2).
2. Updated information on areas where novel influenza virus transmission is suspected or documented is available on the CDC Web site at www.cdc.gov/travel/other/avian_flu_ah5n1_031605.htm and on the WHO Web site at www.who.int/en/.
3. For persons who live in or visit affected areas, close contact includes touching live poultry (well-appearing, sick or dead) or touching or consuming uncooked poultry products, including blood. For animal or market workers, it includes touching surfaces contaminated with bird feces. In recent years, most instances of human infection with a novel influenza A virus having pandemic potential, including influenza A (H5N1), are thought to have occurred through direct transmission from domestic poultry. A small number of cases are also thought to have occurred through limited person-to-person transmission or consumption of uncooked poultry products. Transmission of novel influenza viruses from other infected animal populations or by contact with surfaces contaminated with feces remains a possibility. These guidelines will be updated as needed if alternate sources of novel influenza viruses are suspected or confirmed.
4. Close contact includes direct physical contact, or approach within 3 feet (1 meter) of a person with suspected or confirmed novel influenza.
5. Standard and Droplet Precautions should be used when caring for patients with novel influenza or seasonal influenza (See Infection Control Supplement). Information on infection precautions that should be implemented for all respiratory illnesses (i.e., Respiratory Hygiene/Cough Etiquette) is provided at: www.cdc.gov/flu/professionals/infectioncontrol/resphygiene.htm
6. Hospitalization should be based on all clinical factors, including the potential for infectiousness and the ability to practice adequate infection control. If hospitalization is not clinically warranted, and treatment and infection control is feasible in the home, the patient may be managed as an outpatient. The patient and his or her household should be provided with information on infection control procedures to follow at home (Box 3). The patient and close contacts should be monitored for illness by local public health department staff.
7. Guidance on how to report suspected cases of novel influenza is provided in Laboratory and Surveillance Supplement.
8. The general work-up should be guided by clinical indications. Depending on the clinical presentation and the patient's underlying health status, initial diagnostic testing might include:
    - Pulse oximetry
    - Chest radiograph
    - Complete blood count (CBC) with differential
    - Blood cultures
    - Sputum (in adults), tracheal aspirate, pleural effusion aspirate (if pleural effusion is present) Gram stain and culture
    - Antibiotic susceptibility testing (encouraged for all bacterial isolates)
    - Multivalent immunofluorescent antibody testing or PCR of nasopharyngeal aspirates or swabs for common viral respiratory pathogens, such as influenza A and B, adenovirus, parainfluenza viruses, and respiratory syncytial virus, particularly in children
    - In adults with radiographic evidence of pneumonia, *Legionella* and pneumococcal urinary antigen testing

- If clinicians have access to rapid and reliable testing (e.g., PCR) for *M. pneumoniae* and *C. pneumoniae*, adults and children <5 yrs with radiographic pneumonia should be tested.
- Comprehensive serum chemistry panel, if metabolic derangement or other end-organ involvement, such as liver or renal failure, is suspected See Box 2 for additional details.

9. Guidelines for novel influenza virus testing can be found in Laboratory and Surveillance Supplement. All of the following respiratory specimens should be collected for novel influenza A virus testing: nasopharyngeal swab; nasal swab, wash, or aspirate; throat swab; and tracheal aspirate (for intubated patients), stored at 4° C in viral transport media; and acute and convalescent serum samples.
10. Strategies for the use of antiviral drugs are provided in Vaccine and Antiviral Supplement.
11. Guidelines for the management of contacts in a healthcare setting are provided in Healthcare Planning Supplement.
12. Given the unknown sensitivity of tests for novel influenza viruses, interpretation of negative results should be tailored to the individual patient in consultation with the local health department. Novel influenza directed management may need to be continued, depending on the strength of clinical and epidemiologic suspicion. Antiviral therapy and isolation precautions for novel influenza may be discontinued on the basis of an alternative diagnosis. The following criteria may be considered for this evaluation:
    - Absence of strong epidemiologic link to known cases of novel influenza
    - Alternative diagnosis confirmed using a test with a high positive-predictive value
    - Clinical manifestations explained by the alternative diagnosis
13. Guidance on the evaluation and treatment of suspected post-influenza community-associated pneumonia is provided in Appendix 3.

Figure 2. Case Detection and Clinical Management during the Pandemic Period



Footnotes to Figure 2:

1. Antiviral therapy and isolation precautions for pandemic influenza should be discontinued on the basis of an alternative diagnosis only when both the following criteria are met:
   - Alternative diagnosis confirmed using a test with a high positive-predictive value, and
   - Clinical manifestations entirely explained by the alternative diagnosis
2. Standard and Droplet Precautions should be used when caring for patients with novel influenza or seasonal influenza (Table 4 in Infection Control Supplement). Information on infection precautions that should be implemented for all respiratory illnesses (i.e., Respiratory Hygiene/Cough Etiquette) is provided at: www.cdc.gov/flu/professionals/infectioncontrol/resphygiene.htm
3. Guidance on laboratory testing during the Pandemic Period can be found in Laboratory and Surveillance Supplement. Generally, specimens should include respiratory samples (e.g., nasopharyngeal wash/aspirate; nasopharyngeal, nasal or oropharyngeal swabs, or tracheal aspirates) stored at 4°C in viral transport media.

   Routine laboratory confirmation of clinical diagnoses will be unnecessary as pandemic activity becomes widespread in a community. CDC will continue to work with state health laboratories to conduct virologic surveillance to monitor antigenic changes and antiviral resistance in the pandemic virus strains throughout the Pandemic Period.

4. The decision to hospitalize should be based on a clinical assessment of the patient and the availability of hospital beds and personnel.
5. Guidelines on cohorting can be found in Infection Control Supplement. Laboratory confirmation of influenza infection is recommended when possible before cohorting patients.
6. The general work-up should be guided by clinical indications. Depending on the clinical presentation and the patient's underlying health status, initial diagnostic testing might include:
    - Pulse oximetry
    - Chest radiograph
    - Complete blood count (CBC) with differential
    - Blood cultures
    - Sputum (in adults) or tracheal aspirate Gram stain and culture
    - Antibiotic susceptibility testing (encouraged for all bacterial isolates)
    - Multivalent immunofluorescent antibody testing of nasopharyngeal aspirates or swabs for common viral respiratory pathogens, such as influenza A and B, adenovirus, parainfluenza viruses, and respiratory syncytial virus, particularly in children
    - In adults with radiographic evidence of pneumonia, *Legionella* and pneumococcal urinary antigen testing
    - If clinicians have access to rapid and reliable testing (e.g., PCR) for *M. pneumoniae* and *C. pneumoniae*, adults and children <5 yrs with radiographic pneumonia should be tested.
    - Comprehensive serum chemistry panel, if metabolic derangement or other end-organ involvement, such as liver or renal failure, is suspected See Box 2 for additional details.
7. Guidance on the evaluation and treatment of community acquired pneumonia and suspected post-influenza community-acquired bacterial pneumonia are provided in Appendix 3.
8. Strategies for the use of antiviral drugs are provided in Vaccine and Antiviral Supplement.
9. Guidance on the reporting of pandemic influenza cases is found in Laboratory and Surveillance Supplement.
10. Patients with mild disease should be provided with standardized instructions on home management of fever and dehydration, pain relief, and recognition of deterioration in status. Patients should also receive information on infection control measures to follow at home (Box 4). Patients cared for at home should be separated from other household members as much as possible. All household members should carefully follow recommendations for hand hygiene, and tissues used by the ill patient should be placed in a bag and disposed of with other household waste. Infection within the household may be minimized if a primary caregiver is designated; ideally, someone who does not have an underlying condition that places them at increased risk of severe influenza disease. Although no studies have assessed the use of masks at home to decrease the spread of infection, using a surgical or procedure mask by the patient or caregiver during interactions may be beneficial. Separation of eating utensils for use by a patient with influenza is not necessary, as long as they are washed with warm water and soap. Additional information on measures to limit the spread of pandemic influenza in the home and community can be found in Infection Control and Disease Transmission Supplements.

Figure 3. Management of Community-Acquired Pneumonia during an Influenza Pandemic: Adults

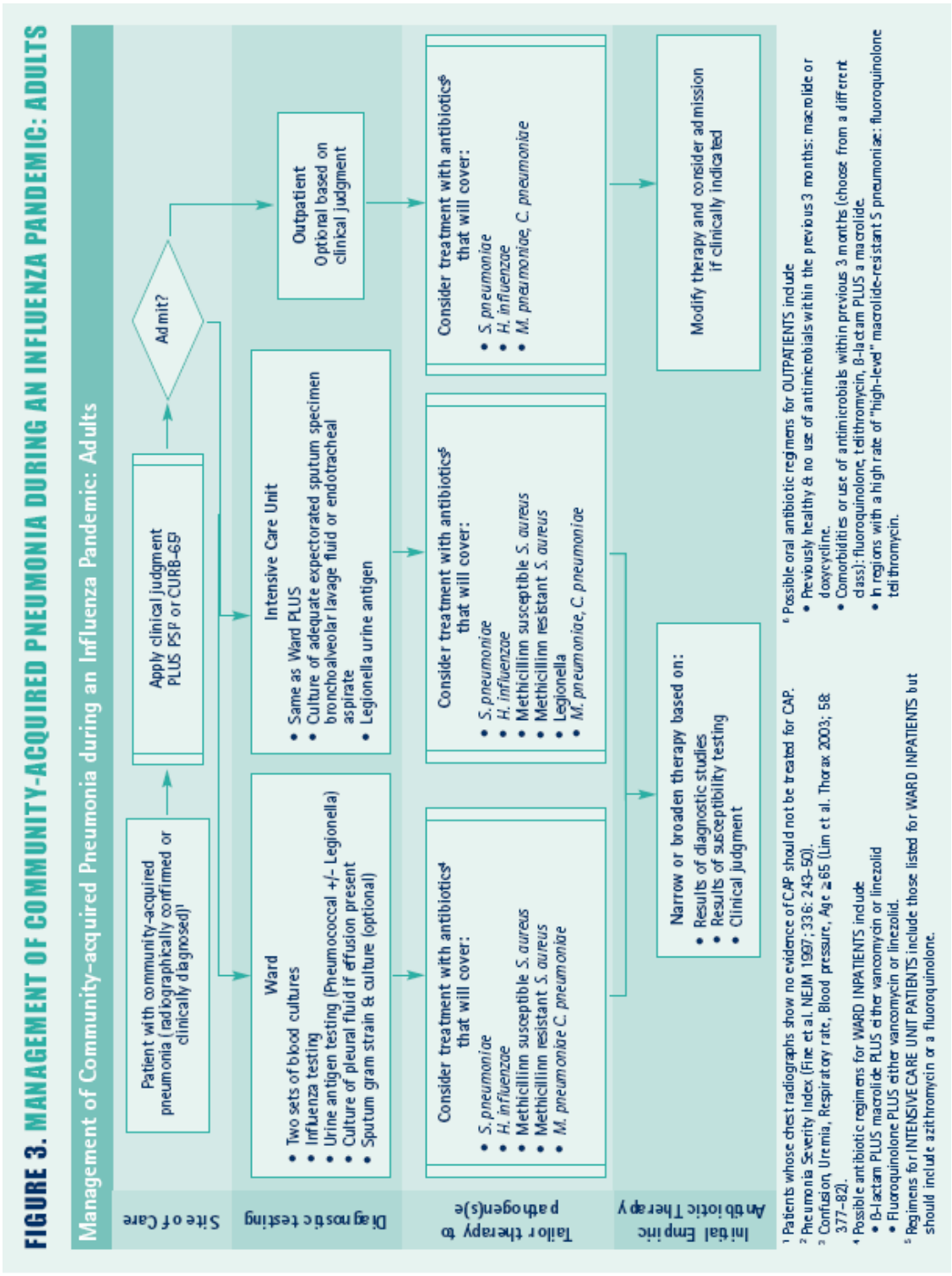
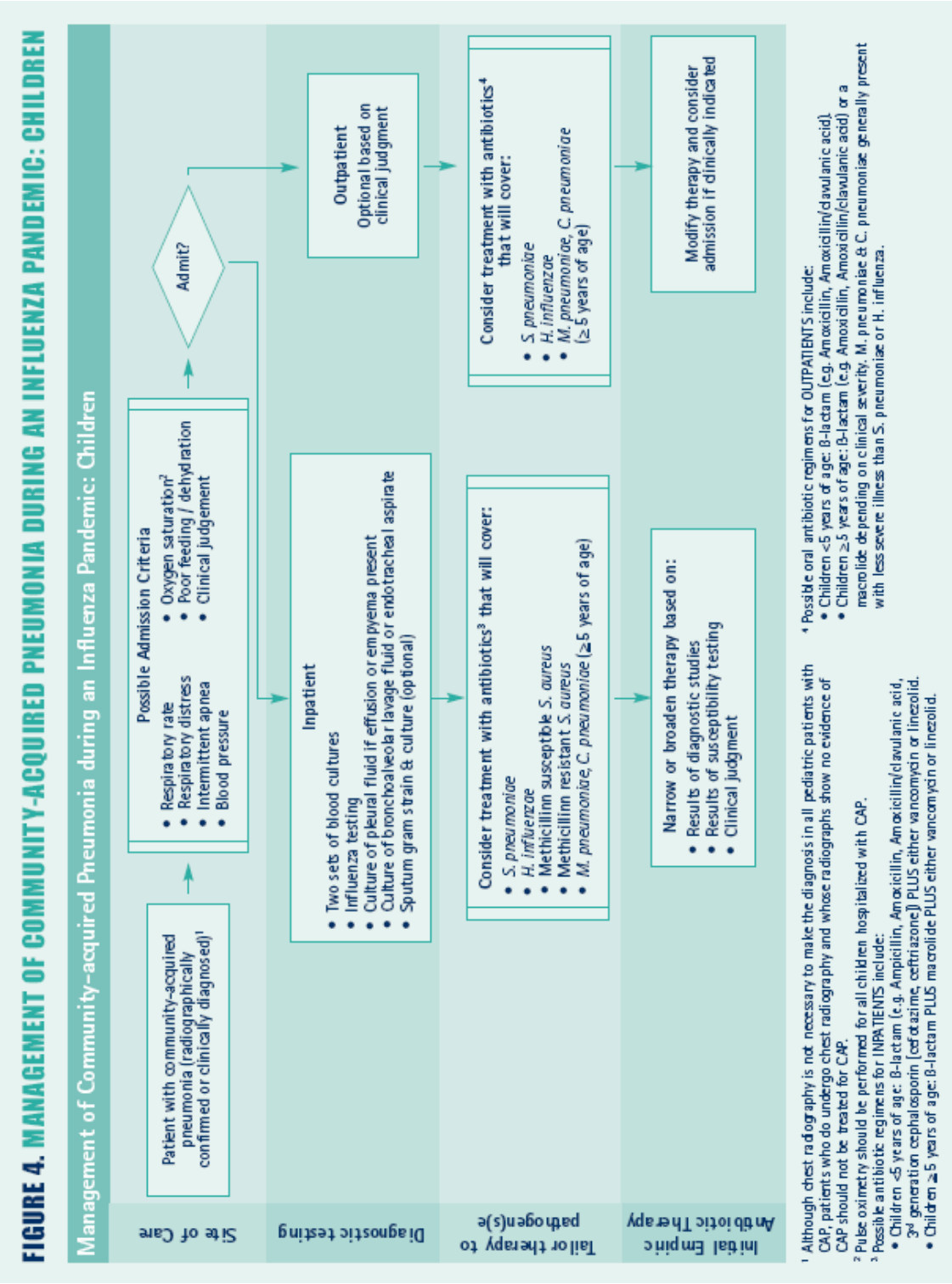


Figure 4: Management of Community Acquired Pneumonia during an Influenza Pandemic: Children



Appendix 1.
Clinical Presentation and Complications of Seasonal Influenza

Although often quite characteristic, the clinical picture of seasonal influenza can be indistinguishable from illness caused by other respiratory infections. The frequent use of non-specific terms such as "flu" and "influenza-like illness" makes the clinical diagnosis of influenza even more indefinite. Even when the diagnosis of influenza is confirmed, management can be challenging, as influenza virus infection can result in subclinical infection, mild illness, uncomplicated influenza, or exacerbation of underlying chronic conditions to fulminant deterioration, and can result in a wide variety of complications.

This appendix provides a brief description of the common presentations and complications of seasonal human influenza. Novel and pandemic influenza viruses might, however, cause quite different clinical syndromes than seasonal influenza. For instance, seasonal influenza-related complications more commonly affect those at the extremes of age, whereas previous pandemics resulted in disproportionate morbidity and mortality in young and previously healthy adults. It will be essential to describe and disseminate the clinical features of novel or pandemic influenza cases as soon as they are identified.

Presentation of Seasonal Influenza

- A typical case of uncomplicated seasonal influenza begins abruptly and is manifested by systemic symptoms such as fever, chills, myalgias, anorexia, headache, and extreme fatigue. Fever typically lasts 2–3 days and usually reaches 38–40°C, but can be higher (particularly in children).

- Respiratory tract symptoms such as nonproductive cough, sore throat, and upper respiratory congestion occur at the same time, although these may be overshadowed by systemic complaints.

- Physical examination typically reveals fever, weakness, mild inflammation of the upper respiratory tract, and rare crackles on lung examination, but none of these findings is specific for influenza.

- In uncomplicated illness, major symptoms typically resolve after a limited number of days, but cough, weakness, and malaise can persist for up to 2 weeks.

- In the elderly and in infants, the presenting signs can include respiratory symptoms with or without fever, fever only, anorexia only, lassitude, or altered mental status. In children, fevers are often higher than in adults and can lead to febrile seizures. Gastrointestinal manifestations (e.g., vomiting, abdominal pain, and diarrhea) occur more frequently in children. Fever or apnea without other respiratory symptoms might be the only manifestations in young children, particularly in neonates.

At times, influenza can be difficult to distinguish from illnesses caused by other respiratory pathogens on the basis of symptoms alone. Fever and cough, particularly in combination, are modestly predictive of influenza in unvaccinated adults, as is the combination of fever, cough, headache, and pharyngitis in children.

Other constitutional signs and symptoms, such as chills, rigors, diaphoresis, and myalgias, are also suggestive. The positive predictive value of any clinical definition is strongly dependent on the level of influenza activity and the presence of other respiratory pathogens in the community.

Routine laboratory findings for seasonal influenza
No routine laboratory test results are specific for influenza. Leukocyte counts are variable. Severe leukopenia and thrombocytopenia have been described in fulminant cases. Leukocytosis of >15,000 cells/mL should raise suspicion for a secondary bacterial process. Comprehensive laboratory testing might reveal other influenza-related complications (see Complications below).

Differential diagnosis
The fever and respiratory manifestations of seasonal influenza are not specific and can occur with several other pathogens, such as respiratory syncytial virus (RSV), parainfluenza viruses, adenoviruses, human metapneumovirus, rhinoviruses, coronaviruses, and *Mycoplasma pneumoniae*.

In contrast to influenza, most of these pathogens do not usually cause severe disease, particularly in previously healthy adults. However, RSV and parainfluenza viruses can lead to severe respiratory illness in young children and the elderly and should be considered in the differential diagnosis if circulating in the community. Even if an alternate etiology is determined, viral or bacterial co-infections can still be a possibility.

Often the clinician can diagnose seasonal influenza with reasonable certainty in the absence of laboratory testing due to the tendency for influenza to occur in community epidemics and to affect persons of all ages. Nevertheless, a definitive diagnosis requires laboratory testing.

Rapid influenza diagnostic tests and immunofluorescence testing using a panel of respiratory pathogens aid in the clinical management of patients with suspected influenza. Further information on diagnostic testing for influenza can be found at http://www.cdc.gov/flu/professionals/labdiagnosis.htm.

Complications
Groups at risk for complications of influenza

The following groups are currently recognized to be at higher risk for complications of seasonal influenza (e.g., hospitalization; death) compared to healthy older children and younger adults (see Prevention and control of influenza: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR 2005; 54: 1-40 http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5408a1.htm).

- Persons aged 65 years and older
- Residents of nursing homes and other chronic-care facilities that house persons of any age who have chronic medical conditions
- Adults and children who have chronic disorders of the pulmonary or cardiovascular systems, including asthma
- Adults and children who required regular medical follow-up or hospitalization during the previous year because of chronic metabolic diseases (including diabetes mellitus), renal

dysfunction, hemoglobinopathies, or immunosuppression (including immunosuppression caused by medications or by infection with human immunodeficiency virus [HIV])
- Children and adolescents (aged 6 months–18 years) who are receiving long-term aspirin therapy (and are therefore at risk for Reye syndrome)
- Pregnant women
- All children aged <2 years
- All persons with conditions that can compromise respiratory function or the handling of respiratory secretions, or that can increase the risk of aspiration

Excluding the last group, in 2003 approximately 85 million persons in the United States belonged to one or more of these target groups.

Types of influenza complications

1. Respiratory exacerbations. Worsening of underlying chronic diseases are the most common serious complications of influenza. Complications are frequently related to underlying respiratory disease, such as chronic obstructive pulmonary disease (COPD). In some cases, typical influenza symptoms might be brief or minimal compared to the exacerbation of the underlying disease, particularly in the elderly.

2. Secondary bacterial pneumonia. This common complication is characterized by an initial improvement in influenza symptoms over the first few days followed by a return of fever, along with a productive cough and pleuritic chest pain. Findings include lobar consolidation on chest x-ray and, in adults, sputum smears positive for leukocytes and bacteria. The most commonly isolated pathogens are *Streptococcus pneumoniae*, *Staphylococcus aureus*, group A Streptococcus, and *Haemophilus influenzae*.

3. Primary influenza viral pneumonia. A prominent feature of previous influenza pandemics, primary influenza viral pneumonia is currently a relatively rare outcome of seasonal influenza in adults. In contrast, children with pneumonia are more likely to have a viral etiology, including influenza than a bacterial cause. Primary influenza pneumonia usually begins abruptly, with rapid progression to severe pulmonary disease within 1–4 days. Physical and radiologic findings are consistent with diffuse interstitial and/or alveolar disease, including bilateral inspiratory crackles on auscultation and diffuse pulmonary infiltrates on chest radiographs. Hypoxia and hemoptysis indicate a poor prognosis, and recovery can take up to 1–2 weeks.

4. Mixed viral-bacterial pneumonia. This is slightly more common than primary viral pneumonia, and, although mixed pneumonia may have a slower progression, the two are often indistinguishable. Bacterial pathogens in mixed infections are similar to those found in secondary bacterial pneumonias.

5. Bronchiolitis due to influenza. This occurs more commonly in children, with a clinical picture similar to that of RSV or parainfluenza virus infections.

6. Croup. Influenza can cause croup (laryngotracheobronchitis) in children, and, although influenza viruses are a less common etiology than other respiratory viruses, the illness can be more severe.

7. Otitis media & sinusitis. Children with influenza can also develop otitis media, due to either direct viral infection or secondary bacterial involvement. Similarly, bacterial sinusitis can develop in older children and adults with influenza.

8. Cardiovascular complications. A range of cardiovascular problems can occur, most commonly as an exacerbation of an underlying condition such as congestive heart failure. Pregnant women and children with congenital heart defects can also experience worsening cardiac function during an influenza illness. Cardiac inflammation, such as myocarditis and pericarditis, can be found occasionally, although clinical manifestations are rare. Available reports suggest that myocarditis might have occurred more frequently during pandemic years. Influenza virus is not typically identified in heart tissue, suggesting that the host inflammatory response might play a role. Although influenza has been associated in rare instances with sudden death possibly due to cardiac arrhythmia, this outcome has been difficult to investigate.

9. Gastrointestinal symptoms. Gastrointestinal involvement is uncommon in adults with seasonal influenza; it is more commonly reported in children. Manifestations can include vomiting and diarrhea, sometimes leading to significant dehydration. Transient hepatic inflammation can occur in rare circumstances.

10. Myositis related to influenza. This is another complication more commonly found in children. It is also more frequently associated with influenza B than with influenza A. Involvement may be limited to pain and weakness of the lower extremities but sometimes can progress to rhabdomyolysis and renal failure.

11. Encephalopathy. Influenza-associated encephalopathy, characterized by an acute alteration in mental status within the first few days of fever onset, is a recently recognized complication of influenza in children. Most reports of influenza-associated encephalopathy have been in Japanese children, but the condition has been reported sporadically in other countries, including the United States. The syndrome can include seizures, neurologic deficits, obtundation, and coma. While most children recover completely, some cases can result in permanent sequelae or death. This condition might be due to an abnormal host inflammatory response without viral infection of the central nervous system.

12. Other neurologic complications. Uncomplicated self-limited febrile seizures can occur with high fever, usually occurring in younger children. Guillain-Barré syndrome and transverse myelitis have been reported to occur in very rare instances after influenza, but no definite etiologic relationship has been established.

13. Reye syndrome. This characterized by an acute encephalopathy combined with hepatic failure in the absence of inflammation in either the brain or the liver. Hepatic involvement includes fatty infiltration, hypoglycemia, and hyperammonemia, whereas neurologic manifestations include cerebral edema, delirium, coma, and respiratory arrest. Reye syndrome was found to be associated with the use of aspirin in children; its incidence has decreased dramatically since the 1980s after aspirin use was discouraged in children.

14. Systemic complications. Seasonal influenza can be associated with systemic symptoms, such as sepsis and shock. Sepsis caused by invasive co-infection with *Staphylococcus aureus*, including methicillin-resistant *S. aureus* (MRSA), or other bacteria, such as *Neisseria meningitidis.* Toxic shock syndrome with bacterial co-infection has also been reported.

Appendix 2.
Clinical Presentation and Complications of Illnesses Associated With Avian Influenza A (H5N1) and Previous Pandemic Influenza Viruses

Human infections with different avian influenza A viruses have emerged and caused mild to severe illness in recent years, including H9N2, H7N7, H7N3, and H7N2. One novel subtype, influenza A (H5N1), has repeatedly caused limited outbreaks of severe and fatal human disease in recent years and therefore has been of particular concern.

Human infection with avian influenza A (H5N1)
The H5N1 subtype first came to widespread public attention in 1997, when a poultry outbreak of highly pathogenic avian influenza A (H5N1) in Hong Kong caused illness in 18 humans. These cases were the first identified instances of direct avian-to-human transmission of an avian influenza A virus that led to severe disease.

Clinical features ranged from asymptomatic infection or mild upper respiratory symptoms to severe pneumonia and death. Most cases presented with fever, headache, malaise, myalgia, sore throat, cough, and rhinorrhea; a few persons also had conjunctivitis or gastrointestinal distress. Seven persons, mostly children, developed only mild upper respiratory infections, whereas 11 developed severe primary viral pneumonia with rapid deterioration. Most patients in this latter group developed lymphopenia; six developed acute respiratory distress syndrome (ARDS), and five developed multi-organ system failure. Other abnormalities included pulmonary hemorrhage, renal dysfunction, liver failure, pancytopenia, hemophagocytosis, and Reye syndrome (with aspirin ingestion). Notably, none of the patients had secondary bacterial pneumonia. Six of the 18 infected persons eventually died.

Avian influenza A (H5N1) resurfaced in Hong Kong in February 2003, in a father and son returning from Fujian Province, China. Both presented with influenza-like symptoms, chest radiograph abnormalities, and lymphopenia. The father's status rapidly deteriorated, and he developed severe lung involvement and hemophagocytosis; the 8-year-old son recovered. Of note, the father's 7-year-old daughter had also died of a pneumonia-like illness while in China, but the cause of her illness was not determined. The boy reported close contact with live chickens during his visit to China, but no definite source for H5N1 was found.

The most recent human outbreak of avian influenza A (H5N1) has been ongoing since December 2003. This outbreak has been associated with an extensive H5N1 epizootic among poultry in Asia. Transmission continues to be predominantly from birds to humans, although a few instances of limited human-to-human transmission have been suspected.

Reports published from Vietnam and Thailand describe the early confirmed H5N1 cases from this outbreak. These reports characterize human illness with avian influenza A (H5N1) virus infection as a primarily respiratory febrile illness that progresses to severe disease in a high proportion of cases. Among 10 Vietnamese patients,[1] all were previously healthy children or young adults (mean age, 13.7 years) who presented to medical attention with fever, cough, and dyspnea. None of the patients had other respiratory symptoms, such as sore throat or rhinorrhea, but seven developed diarrhea. Significant lymphopenia was observed in all 10 cases, and moderate thrombocytopenia occurred. All 10 had marked abnormalities on chest radiograph, and eight patients—all of whom eventually died—required mechanical ventilation for respiratory failure. Respiratory cultures suggested bacterial pneumonia in two patients.

Of 12 cases described from Thailand,[2] seven were aged <14 years, and all but one were previously healthy. All of the patients developed fever, cough, and dyspnea, and six patients were reported with myalgia and diarrhea. Decreased leukocyte counts were reported in seven cases, thrombocytopenia occurred in four cases, and increased serum liver enzymes were found in eight. All patients had negative blood cultures. They all had abnormal chest radiographs; nine developed respiratory failure with ARDS, whereas five developed cardiac failure, four had renal failure, and eight ultimately died. In the Vietnamese and Thai cases, respiratory deterioration occurred a median of 5 days after symptom onset, but the range was quite wide.

Whereas all patients described above presented with pulmonary symptoms, subsequently published case reports suggest that other clinical syndromes can occur with H5N1 infection.[3,4,5] In one report, a 39-year-old female with confirmed H5N1 from Thailand was initially admitted with symptoms of fever, vomiting, and diarrhea, and was found to have significant lymphopenia. She developed shortness of breath approximately 12 days after illness onset and soon progressed to ARDS and death.

A 4-year-old male from Vietnam presented for medical attention with severe diarrhea, developed acute encephalitis with coma, and died soon thereafter. Although avian influenza A (H5N1) was later detected in throat, stool, serum, and cerebrospinal fluid specimens, the patient had no respiratory symptoms at presentation. This patient's 9-year-old sister died of a similar illness a few days before his illness began, but no H5N1 testing was performed. Asymptomatic H5N1 infection, detected by seroconversion, has been reported. Updated information on avian influenza can be found at http://www.who.int/csr/disease/avian_influenza/en/.

Illnesses associated with previous pandemic viruses

Since most people do not have previous immunity to novel influenza A viruses, an influenza pandemic results in an increased rate of severe disease in a majority of age groups. Nevertheless,

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[1] Tran TH, Nguyen TL, Nguyen TD, Luong TS, Pham PM, Nguyen VC, et al. Avian influenza A (H5N1) in 10 patients in Vietnam. N Engl J Med. 2004;350:1179-88.

[2] Chotpitayasunondh T, Ungchusak K, Hanshaoworakul W, Chunsuthiwat S, Sawanpanyalert P, Kijphati R, et al. Human disease from influenza A (H5N1), Thailand, 2004. Emerg Infect Dis. 2005;11:201-9.

[3,4,5] de Jong MD, Bach VC, Phan TQ, Vo MH, Tran TT, Nguyen BH, et al. Fatal avian influenza A (H5N1) in a child presenting with diarrhea followed by coma. N Engl J Med. 2005;352:686-91.

Apisarnthanarak A, Kitphati R, Thongphubeth K, Patoomanunt P, Anthanont P, Auwanit W, et al. Atypical avian influenza (H5N1). Emerg Infect Dis 2004;10:1321-4

Beigel JH, Farrar J, Hayden FG, Hyer R, de Jong MD, Lochindrat S, et al. Avian influenza A (H5N1) infection in humans. N Eng J Med. 2005 Sep 29;353(13):1374-85.

the three pandemics of the past century demonstrated significant variability in terms of morbidity.

The 1918–19 pandemic was particularly notable in affecting young, healthy adults with severe illness. A significant proportion of patients developed fulminant disease, accompanied by a striking perioral cyanosis, leading to death within a few days. Postmortem examinations in these patients frequently revealed denuding tracheobronchitis, pulmonary hemorrhage, or pulmonary edema. Others survived the initial illness, only to die *of* a secondary bacterial pneumonia, usually due to *Streptococcus pneumoniae*, *Staphylococcus aureus*, group A Streptococcus, or *Haemophilus influenzae*.

The clinical features of the subsequent pandemics of 1957–58 and 1968–69 were also typical of influenza-like illness, including fever, chills, headache, sore throat, malaise, cough, and coryza, but were milder compared to the 1918–19 pandemic. On a population level, the impact of influenza in 1957–58 was only one-tenth that observed in 1918–19, and the excess death rate in 1968–69 was only half that observed during 1957–58. However, death rates were elevated among the chronically ill and the elderly, and the occurrence of severe complications, such as primary viral pneumonia, was notably increased in healthy young adults during the 1957–58 pandemic, particularly in pregnant women.

Implications for the next pandemic

The characteristic clinical features of the next influenza pandemic cannot be predicted. It is reasonable to assume that most affected persons will have the typical features of influenza (e.g., fever, respiratory symptoms, myalgia, malaise). However, past pandemics have varied considerably with regard to severity and associated complications.

Illnesses caused by novel influenza viruses such as avian influenza A (H5N1) might predict the potential characteristics of pandemic influenza, but H5N1 has not adapted to spread easily among humans, and its presentation and severity might change as the virus evolves. Even as the next pandemic begins and spreads, the characteristic features might change, particularly if successive waves occur over several months.

Given this potential for a dynamic clinical picture, it will be important for clinicians and public health partners to work together to disseminate updated and authoritative information to the healthcare community on a regular basis.

Appendix 3.
Guidelines For Management of Community-Acquired Pneumonia, Including Post-Influenza Community-Acquired Pneumonia

Rationale

Post-influenza bacterial community-acquired pneumonia will likely be a common complication during the next pandemic and might affect approximately 10% of persons with pandemic influenza, based on data from previous influenza pandemics. Assuming that pandemic influenza will affect about 15%–35% of the U.S. population, approximately 4.4 to 10.2 million cases of post-influenza bacterial community-acquired pneumonia could occur.

Post-influenza bacterial community-acquired pneumonia often presents as a return of fever, along with a productive cough and pleuritic chest pain, after an initial improvement in influenza symptoms over the first few days. Findings include lobar consolidation on chest x-ray and, in adults, sputum smear positive for leukocytes and bacteria. As with other bacterial infections, leukocytosis with increased immature forms may be present, but this finding is neither sensitive nor specific.

The most common etiologies of post-influenza bacterial pneumonia are *Streptococcus pneumoniae*, *Staphylococcus aureus*, group A Streptococcus, and *Haemophilus influenzae*.

Primary viral pneumonia, with abrupt onset and rapid progression, is more common than bacterial pneumonia in children, yet rare in adults. Physical and radiologic findings in viral pneumonia are consistent with interstitial and/or alveolar disease and include bilateral inspiratory crackles and diffuse infiltrates.

Mixed viral-bacterial pneumonia is slightly more common than primary viral pneumonia, but they are often indistinguishable. Bacterial pathogens in mixed infections are similar to those found in secondary bacterial pneumonias.

Droplet and Standard Precautions are currently recommended for community-acquired pneumonia of bacterial etiology.[1]

Treatment of community-acquired pneumonia, including post-influenza bacterial community-acquired pneumonia will pose challenges for clinicians during a pandemic. Secondary bacterial pneumonia following influenza virus infection will be difficult to distinguish from community-acquired pneumonia that is not preceded by influenza.

Current guidelines for the treatment of adult community-acquired pneumonia (CAP) during the Interpandemic Period de-emphasize the use of diagnostic testing for pathogen-directed treatment and favor empiric therapy with safe and effective broad-spectrum antibacterials, especially extended-spectrum macrolides and fluoroquinolones. However, these antibacterials will likely be in short supply during a pandemic.

[1] Centers for Disease Control and Prevention. Guidelines for preventing health-care-associated pneumonia, 2003 recommendations of CDC and the Healthcare Infection Control Practices Advisory Committee. Respir Care. 2004;49(8):926-39.

The guidelines in this appendix are therefore designed to assist clinicians in managing patients with community-acquired pneumonia, including post-influenza bacterial community-acquired pneumonia, in a setting of high patient volume and limited clinical resources, where the pressure to treat empirically will likely be even greater than during the Interpandemic Period.

These recommendations are from the November 2005 HHS Pandemic Influenza Plan (http://www.hhs.gov/pandemicflu/plan/pdf/HHSPandemicInfluenzaPlan.pdf).
For adults, the guidance draws heavily from the current draft guidelines for the management of CAP developed jointly by the Infectious Diseases Society of America (IDSA)[2] and the American Thoracic Society (ATS).[3] For children, the guidance incorporates recommendations from the British Thoracic Society (BTS),[4] a published review[5] and expert opinions

Prevention
Preventing pneumoccal pneumonia by maximizing vaccination coverage against *Streptococcus pneumoniae for at risk individuals is* important during the Interpandemic, Pandemic Alert, and Pandemic Periods. Current guidelines on the use of the 23-valent pneumococcal polysaccharide vaccine among adults[6] and the 7-valent pneumococcal conjugate vaccine among children[7] are available.

Site of care: inpatient versus outpatient
Adults
IDSA-ATS draft guidelines recommend the use of severity scores, such as the Pneumonia PORT Severity Index (PSI) and the CURB-65 system, to determine which patients can be safely treated as outpatients (Tables 2–5). The use of these or other similar systems could be extremely important during the next pandemic, as hospital beds will be in short supply. However, these systems should be used as guidance and not replace the judgment of the individual clinician.

Children
Current guidelines provide indicators for hospitalization of children with CAP. For infants, the indications include temperature >38.5 C, respiratory rate (RR) >70 breaths per minute, chest retractions (indrawing), nasal flaring, hypoxia, cyanosis, intermittent apnea, grunting, and poor feeding. Indications for hospitalization among older children include temperature >38.5 C, RR >50, chest retractions, nasal flaring, hypoxia, cyanosis, grunting, and signs of dehydration.

As with pandemic influenza, the decision to hospitalize for post-influenza bacterial community-acquired pneumonia during the Pandemic Period will rely on the physician's clinical assessment of the patient as well as availability of personnel and hospital resources. Although an unstable

[2] Mandell LA, Bartlett JG, Dowell SF, File TM Jr, Musher DM, Whitney C; Infectious Diseases Society of America. Update of practice guidelines for the management of community-acquired pneumonia in immunocompetent adults. Clin Infect Dis. 2003; 37(11):1405-33.
[3] Niederman MS, Mandell LA, Anzueto A, Bass JB, Broughton WA, Campbell GD, et al. American Thoracic Society. Guidelines for the management of adults with community-acquired pneumonia. Diagnosis, assessment of severity, antimicrobial therapy, and prevention. Am J Respir Crit Care Med. 2001;163(7):1730-54.
[4] British Thoracic Society Standards of Care Committee. British Thoracic Society guidelines for the management of community acquired pneumonia in childhood. Thorax. 2002;57(suppl 1):i1-24.
[5] McIntosh, K. Community-acquired pneumonia in children. N Engl J Med. 2002;346:429-37.
[6] CDC. Prevention of pneumococcal disease: recommendations of the Advisory Committee on Immunization Practices (ACIP). MMWR Morb Mortal Wkly Rep. 1997;46(RR-8).
[7] Prevention of pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices. MMWR Morb Mortal Wkly Rep. 2000;49(RR-9).

patient will be considered a high priority for admission, patients with certain high-risk conditions (see Appendix 1) might also warrant special attention. Home management with follow-up might be appropriate for well-appearing young children with fever alone.

Diagnostic testing

Adults

Generally, the etiologies associated with CAP during the Interpandemic Periods will continue to occur during a pandemic. Familiarity with the appropriate use of available diagnostic tests is therefore a key feature of clinical preparedness.

1. Look for *S. pneumoniae* and *S. aureus*. Draft IDSA-ATS guidelines recommend obtaining appropriate specimens for etiologic diagnosis whenever such an etiology would alter clinical care. Since the most common etiologies of post-influenza bacterial community-acquired pneumonia [*S. pneumoniae* and *S. aureus*, including community-acquired methicillin-resistant *S. aureus* (CA-MRSA)] are treated differently, diagnostic testing should be performed to the extent feasible to distinguish among these pathogens.

2. Do additional tests for hospitalized patients.
    a. Blood cultures, pneumococcal urine antigen testing, and pleural fluid aspiration with Gram stain and culture should be considered.
    b. Since sputum Gram stain and culture is highly dependent on patient and technical conditions, these are considered optional for hospitalized but non-severe patients.
    c. For patients admitted to an ICU, consider aspiration of endotracheal secretions for Gram stain and bacterial culture.

Children

Diagnostic studies for identifying bacterial pneumonia in young children are severely limited.

1. Blood cultures should be obtained from all children suspected of having post-influenza bacterial community-acquired pneumonia.
2. Sputum samples are rarely useful in children. However, if tracheal or pleural fluid aspirates are available, they should be submitted for Gram stain and bacterial culture.
3. If pleural effusions are present, they should be aspirated and submitted for Gram stain and culture.
4. Test antibiotic susceptibility testing of any bacterial isolates to direct treatment, where feasible.

Antibiotic treatment

Adults and children

Antibiotics will likely be in short supply during the Pandemic Period, particularly those needed to treat CAP. Therefore, use of empiric therapy for all persons with post-influenza bacterial community-acquired pneumonia may not be feasible.

1. Antimicrobial therapy is best managed by culture and susceptibility testing of appropriate clinical specimens, and by awareness of local antibiotic susceptibility patterns. (See Figures 1 and 2 for additional clinical management algorithms and information.)
2. A history of a preceding influenza-like illness, especially when pandemic influenza is circulating in the community, might help to select those patients more likely to have viral rather than bacterial respiratory infection.
3. Empiric therapy should be directed toward the most likely etiologies of post-influenza bacterial community-acquired pneumonia.

4. Concurrent antiviral treatment should also be considered, depending on the timing and presentation of illness, the clinical status of the patient, and the availability of antivirals (see Vaccine and Antiviral Supplement).

Clinical Guidelines Supplement. Appendix 3. Table 2.
Pneumonia PORT Severity Index (PSI) Calculation

Patient Characteristic	Points Assigned
Demographic Factor	
Age Male Female	Number of years Number of years–10
Nursing home resident	+10
Comorbid illnesses	
Neoplastic disease	+30
Liver disease	+20
Congestive heart failure	+10
Cerebrovascular disease	+10
Renal disease	+10
Physical examination finding	
Altered mental status	+20
Respiratory rate >30 breaths/minute	+20
Systolic blood pressure <90 mm Hg	+20
Temperature <35 C or >40 C	+15
Pulse >125 beats/minute	+10
Laboratory and /or radiographic finding	
Arterial pH <7.35	+30
Blood urea nitrogen >30 mg/dl	+20
Sodium <130mmol/l	+20
Glucose >250 mg/dl	+10
Hematocrit <30%	+10
Hypoxemia: <90% by pulse oximetry OR <60mm Hg by arterial blood gas	+10
Pleural effusion on baseline radiograph	+10

Clinical Guidelines Supplement. Appendix 3. Table 3.
Pneumonia Severity Index Risk Classification

PSI Risk Class	Characteristics and Points	Recommended Site of Care
I	Age >50 years + no comorbid conditions, normal range vital signs, normal mental status	Outpatient
II	<70	Outpatient
III	71–90	Outpatient / Brief inpatient
IV	91–130	Inpatient
V	130	Inpatient

Clinical Guidelines Supplement5. Appendix 3. Table 4.
CURB-65 Scoring System

Characteristic	Points
Confusion1	+1
Urea >7mmol/l (20mg/dl)	+1
Respiratory rate >30 breaths per minute	+1
Blood pressure (Systolic <90 or diastolic <60 mm Hg)	+1
Age >65 years	+1

1 Based on a specific mental test or disorientation to person, place, or time.

Clinical Guidelines Supplement. Appendix 3. Table 5.
Recommended site of care based on CURB-65 system

Number of Points	Recommended Site of Care
0–1	Outpatient
2	Admit to medical ward
3–5	Admit to medical ward or ICU

Appendix 4. Clinician Fact Sheet: Influenza

Epidemiology

- **Human** disease is caused by influenza A or influenza B viruses
- Ongoing minor antigenic changes require yearly vaccination in the fall
- Knowing the currently circulating strain aids in decisions regarding antiviral treatment and prophylaxis

Clinical Presentation

- High fever, chills, prostration, muscle aches, sore throat, coryza, cough; at times, also vomiting and diarrhea

Differential Diagnosis

- Febrile respiratory illnesses such as bacterial pneumonia, mycoplasma, adenovirus, avian influenza (e.g. influenza A H5N1), and SARS

Laboratory

- Rapid testing of nasopharyngeal swabs for influenza
- Consider NP swab for respiratory viral culture (if positive, allows for further typing of isolate)
- Do not order routine viral **culture** if novel influenza A virus infection is suspected

Infection control

- Droplet precautions (mask within 3-6 feet)
- Routine standard precautions and good handwashing before & after patient contact

Treatment & Prophylaxis

- Antivirals shorten the course of illness when given within the first 1-2 days of influenza symptoms
- CDC recommended against the use of amantadine & rimantadine for the 2005-2006 and the 2006-2007 influenza seasons

	Amantadine (Symmetrel®)	**Rimantadine** (Flumadine®)	**Oseltamivir** (Tamiflu®)	**Zanamivir** (Relenza®)
Effective for Influenza A	**NOT RECOMMENDED**		**Yes**	**Yes**
Effective for Influenza B	**No**	**No**	**Yes**	**Yes**
Mode	**Oral**	**Oral**	**Oral**	**Inhaled**
Treatment	**≥ 1 y.o.**	**≥ 13 y.o.**	**≥ 1 y.o.**	**≥ 7 y.o.**
Prophylaxis	**≥ 1 y.o.**	**≥ 1 y.o.**	**≥ 1 y.o.**	**Not licensed – 2006 Updated information in ACIP Influenza Recommendations**

Follow CDC recommendations for ages and contraindications

July 2006 ACIP Recommendations on "Prevention and Control of Influenza, http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5510a1.htm?s_cid=rr5510a1_e]

Remember Pneumovax® or Prevnar® pneumococcal vaccine for high-risk individuals.

Influenza Vaccine Recommendations for 2005-2006 season

Inactivated intramuscular shot [Multiple manufacturers]:

1) Ages ≥ 50 y.o.
2) All children ages 6 mo.-23 mo.
3) Household contacts and out-of-home caretakers of infants < age 6 mo.
4) Ages 2 y.o.-64 y.o. with a chronic medical conditions (e.g. heart disease, lung disease, asthma, diabetes, kidney disease, immunosuppression, etc.)
5) Pregnant during influenza season.
6) Children age 6 mo.-18 y.o. on chronic aspirin therapy.
7) Health care workers (HCW) with direct patient care.
8) Residents in nursing home or long-term care facility.
9) **Anyone** wishing to reduce their risk of influenza.

Live attenuated influenza vaccine (LAIV) [FluMist™]:

- Healthy, nonpregnant people ages 5 y.o. through 49 y.o., including close contacts of infants and many health care workers

Pediatric pointers

- Children aged 6 months to less than 9 years old receiving any influenza vaccine for the first time need two doses of vaccine administered at least one month apart..
    - Two inactivated shots should be spaced ≥ 4 weeks apart
    - Two LAIV doses, given only to those children age five years to less than nine years, should be separated by 6-10 weeks
- Notify local or county health department for pediatric influenza deaths.

Staphylococcal and MRSA disease associated with influenza

- MRSA is becoming a community-acquired infection
- Coagulase positive *Staphylococcus* secondary respiratory infections are more likely with influenza
- During the 2003-2004 season, CDC reported severe illness and death associated with influenza and MRSA
- ➢ Physicians caring for patients who have influenza and worsening respiratory status requiring IV antibiotics should consider using **vancomycin** for staphylococcal coverage until culture results are available and/or clinical improvement occurs
- Many oral antibiotics do not cover MRSA
- Oral antibiotics that may be effective against MRSA
    - Trimethoprim-sulfamethoxazole
        - Poor against *Streptococcus pneumoniae*
        - Avoid in pregnancy
    - Clindamycin (Good against *Streptococcus pneumoniae*)

For More Information

- KDPH Web site (http://chfs.ky.gov/dph/default.htm)
- Centers for Disease Control and Prevention Web site at www.cdc.gov/flu
- MMWR July 29, 2005 "Treatment and Control of Influenza" at
- http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5408a1.htm
- July 2006 ACIP Recommendations on "Prevention and Control of Influenza, http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5510a1.htm?s_cid=rr5510a1_e]

Appendix 5. Clinician Fact Sheet: Antivirals

Four antiviral drugs are licensed for treatment and chemoprophylaxis

- Antivirals shorten the course of illness when given within the first 1-2 days of influenza symptoms
- Avoid antivirals in pregnant women unless benefit outweighs risk
- Though usually effective for influenza A, this season amantadine and rimantadine are not recommended in the U.S. due to high levels of resistance

	Amantadine (Symmetrel®)	**Rimantadine** (Flumadine®)	**Oseltamivir** (Tamiflu®)	**Zanamivir** (Relenza®)
Effective for Influenza A	**NOT RECOMMENDED**		**Yes**	**Yes**
Effective for Influenza B	**No**	**No**	**Yes**	**Yes**
Mode	**Oral**	**Oral**	**Oral**	**Inhaled**
Treatment	**≥ 1 y.o.**	**≥ 13 y.o.**	**≥ 1 y.o.**	**≥ 7 y.o.**
Prophylaxis	**≥ 1 y.o.**	**≥ 1 y.o.**	**≥ 1 y.o.**	**N/A --2006 Updated information in ACIP Influenza Recommendations**

Priority groups for treatment with antiviral medicines

- Any person with a potentially life-threatening influenza-related illness
- Any person at high risk for serious complications of influenza and who is within the first 2 days of illness onset

Priority groups for chemoprophylaxis with antiviral medicines

- All residents and workers during an institutional outbreak
- All persons at high risk of serious influenza complications if they are exposed to a known or suspected case of influenza

Consider antiviral use in these patients if local supplies are adequate:

Chemoprophylaxis

- Persons in communities where influenza viruses are circulating (influenza outbreak usually lasts 6-8 weeks)
- Persons at high risk of serious complications who cannot get vaccinated. Persons at high risk of serious complications who have been vaccinated but have not had time to mount an immune response to the vaccine. In adults, chemoprophylaxis should occur for 2 weeks after vaccination.
- Persons with immunosuppressive conditions who are not expected to mount an adequate antibody response to influenza vaccine.
- Heath-care workers with direct patient care responsibilities who have not been vaccinated

Treatment

- Infected adults and children aged ≥1 year who do not have conditions placing them at high risk for serious complications secondary to influenza infection.

Length of Antiviral Treatment and Chemoprophylaxis

	Treatment Length	**Chemoprophylaxis Length**		
		After exposure	Institutional outbreak	After vaccine**
Amantadine	**NOT RECOMMENDED (ACIP 2006)**			
Rimantadine				
Oseltamivir	5 days	7 days	Until outbreak over	2 weeks
Zanamivir		N/A	N/A	N/A

*Until afebrile 1-2 days ** If antiviral prophylaxis is desired for high-risk individuals during the time immunity is developing

Pediatric Pointers

- Children ≤ 9 years old who have never had an influenza vaccine need 2 doses of influenza vaccine, ≥ 1 month apart to be optimally protected. Therefore, if a high-risk child is vaccinated when there is influenza in the community, antiviral prophylaxis may need to be continued for 6 weeks for optimal protection.
- For pediatric antiviral use where no liquid formulation is available, open the capsule or crush the tablet, and give the appropriate dose in cherry syrup.

ANTIVIRAL MEDICINES

Amantadine [100 mg capsule; 50 mg/5 mL syrup] - **NOT RECOMMENDED (ACIP 2006)**

Rimantadine [100 mg tablet; 50 mg/5 mL syrup] -- **NOT RECOMMENDED (ACIP 2006)**

Oseltamivir (Tamiflu®) [75 mg tablet; 60 mg/5 mL suspension]

- Treatment and prophylaxis of influenza A & B in ≥ 12 months old.
- Treatment: 75 mg PO **twice daily** for 5 days.
- Lower dose in children based on weight:
  - ≤ 15 kg, 30 mg BID;
  - >15-23 kg, 45 mg BID;
  - >23-40 kg, 60 mg BID;
  - >40 kg, 75 mg PO BID.
- Prophylaxis: 75 mg PO **once daily**
- Side effects: nausea & vomiting
- Reduce dose to 75 mg every other day when CrCl 10-30 mL/min
-

Zanamivir (Relenza®) [Inhaler]

- Treatment of influenza A & B in ≥ 7 years of age.
- Inhalation (10 mg) twice daily for 5 days.
- Side effects: Bronchospasm

For more detailed information about each antiviral medication

See http://www.cdc.gov/flu/professionals/treatment

Appendix 6.
Respiratory Etiquette Poster